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Brief Communication

EFFECTS OF ETHIOFOS (WR-2721) AND RADIATION ON MONKEY VISUAL DISCRIMINATION PERFORMANCE

V. BOGO*, C. G. FRANZ*, A. J. JACOBS†, J. F. WEISS† and R. W. YOUNG‡

**Behavioral Sciences and † Radiation Biochemistry Departments, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145, U.S.A.*

‡Radiation Policy Division, Radiation Sciences Directorate, Defense Nuclear Agency, Washington, DC 20305-1000, U.S.A.

WR-2721 (ethiofos) is a promising protector against radiation-induced lethality and may be useful in cancer radiotherapy (Davidson *et al.*, 1980). However, ethiofos also produces nausea, vomiting, diarrhea, and hypotension, which implies severe behavioral consequences (Bogo *et al.*, 1985). We studied the effects of ethiofos on behavior in monkeys and its ability to mitigate early transient incapacitation (ETI). ETI is the abrupt cessation of performance (for at least 1 min) following rapidly delivered, high doses of radiation and usually occurs 5 – 10 min after irradiation and lasts for 1 – 15 min (Bogo, 1988a).

Male rhesus (*Macaca mulatta*) monkeys ($N = 24$) were obtained from the Joint Services Primate Breeding Colony, Naval Aerospace Medical Research Laboratory, Pensacola, Florida, and quarantined 60 d for evaluation, tuberculosis testing, and stabilization. Monkeys were maintained in conventional stainless steel, wall-mounted cages in rooms maintained at 72 ± 2°F, with 50% ± 10% relative humidity using 100% conditioned fresh air at 12 air changes per hr. They were provided commercial monkey chow and hyperchlorinated tap water *ad libitum*, and were kept on a 12 hr light/12 hr dark, full-spectrum light cycle with no twilight.

Monkeys seated in plastic chairs were exposed to a TRIGA reactor pulse (50 msec) of neutron/gamma radiation (ratio 0.4). The doses were 14, 16, 22, and 24 Gy. A 22 Gy pulse was used in the ethiofos/radiation condition because it was known to be 90% effective in producing ETI in monkeys performing the speed stress visual discrimination task (SSVDT) (Bogo *et al.*, 1987). Since the ETI dose was well above the $LD_{50/30}$ of 6 Gy for a monkey, ethiofos was not expected to offer any protection from lethality. Ethiofos was given i.v. (saphenous vein) at least 30 min before irradiation. The 200 mg/kg dose was diluted in 60 cc saline and injected with an infusion pump over 5 min.

Performance was assessed with either a visual discrimination task (VDT) or an SSVDT. In these shock avoidance tasks, trained monkeys discriminated between a circle and a square (always the correct choice) randomly presented every 10 s on backlit press-plates. Maximum response time in the VDT was 5.0 s, and 0.7 s or less in the SSVDT. Performance was assessed 15 min before and after ethiofos, during radiation exposure, and for 90 min after irradiation. The test measures were (a) ETI 90 min following radiation, (b) percent correct choice following ethiofos and/or radiation, (c) emesis after ethiofos and/or radiation, and (d) time to death.

In the repeat-measure study, the same six monkeys (mean weight 8.3 kg) were tested on the SSVDT as follows: (a) sham ethiofos (saline)/sham radiation (baseline control), (b) ethiofos/sham radiation, and (c) ethiofos/radiation. A three week interval was allowed between tests. At the time of the study the number of large, trained monkeys was limited, and no concurrent radiation-only control group existed to illustrate ETI. Radiation-only controls were obtained from the Armed Forces Radiobiology Research Institute's Primate Behavioral Data Base in smaller but similarly handled monkeys (weight 3.7 kg) (Franz *et al.*, 1981). The 14 and 16 Gy irradiated monkeys performed the SSVDT, and the 24 Gy irradiated monkeys performed the VDT. All monkeys were monitored before and after exposure to record incidence of emesis and were

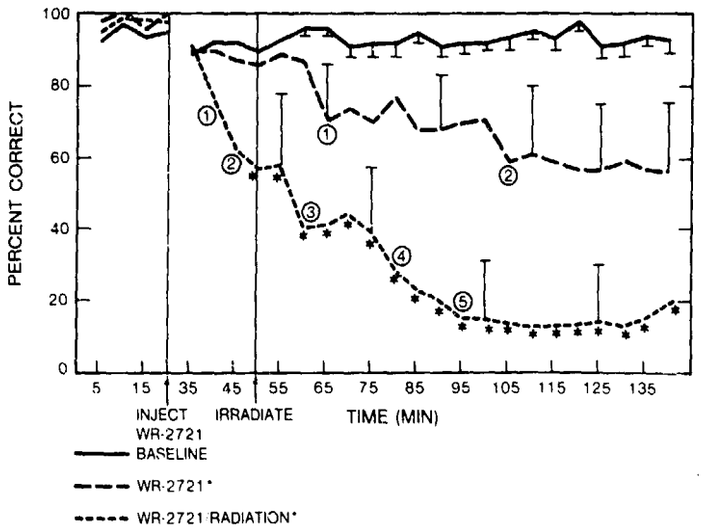

FIG. 1. Baseline, post-ethiofos, and post-ethiofos radiation performance on the SSVDT. Circles show the number of subjects with ETI. Significant effects compared with controls are shown with asterisks ($p < 0.05$). $N = 6$.

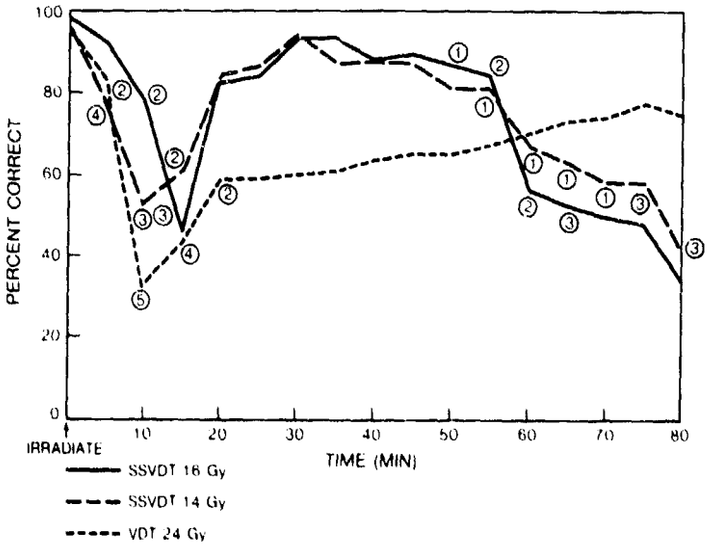

FIG. 2. Radiation control conditions for Fig. 1. Performance on the SSVDT after 14 and 16 Gy radiation, and performance on the VDT after 24 Gy radiation. Circles show the number of subjects with ETI. $N = 6$ group.

monitored until death. Percent correct performance was analyzed by two-way ANOVAs. Chi-square analysis was used to compare incidence of ETI and emesis.

In the repeat-measure conditions, performance during the post-ethiofos test period was significantly below the same-subject baseline, ranging from 25% to 30% below baseline at 45 and 85 min posttreatment, respectively (Fig. 1). Performance of the ethiofos/radiation condition was significantly below both the same-subject baseline and ethiofos conditions after treatment. The decrements ranged from 35% below baseline 10 min after irradiation to 80% below baseline 45 min after exposure. Both the ethiofos and ethiofos/radiation conditions were overall significantly below the same-subject baseline.

In the radiation-only conditions, performance dropped an average of 56%, 10−15 min postexposure (Fig. 2). Performance in the 14 and 16 Gy conditions recovered to 15% below control after 20 min postexposure, while recovery was more gradual in the 24 Gy condition, to 25% below control at 70 min. All radiation-only conditions in Fig. 2 were significantly below the baseline condition in Fig. 1.

The incidence of ETI was significantly greater in the ethiofos/radiation condition (83%) than ethiofos alone (33%). The incidence of emesis did not differ significantly between the combined and ethiofos-alone conditions (42%). The time until death did not differ significantly between the monkeys irradiated with 24 Gy alone and those treated with ethiofos and irradiated with 22 Gy, i.e. average time to death was 24 hr.

Ethiofos produced a decrement in the SSVDT and offered no protection against radiation-induced ETI; performance was worse in the combined condition than in either the ethiofos or radiation conditions alone. These findings are similar to those previously reported in rats performing a motor function task (Bogo *et al.*, 1985). Since ethiofos is behaviorally toxic in two animal models, future work will focus on either reducing its behavioral toxicity or searching for other effective radioprotectors with less toxic effects on behavior (Bogo, 1988b).

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